Notic of Allowability	Application No.	Applicant(s)	
	10/622,064	BACHMANN ET AL.	
	Examiner	Art Unit	
	Mary E. Mosher, Ph.D.	1648	

-- The MAILING DATE of this communication app ars on the cover sh et with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☒ This communication is responsive to *10/15/2004*.

2. ☒ The allowed claim(s) is/are *116-153*.

3. ☒ The drawings filed on *20 May 2002* are accepted by the Examiner.

4. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
   a) ☐ All b) ☐ Some* c) ☐ None of the:
      1. ☐ Certified copies of the priority documents have been received.
      2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
      3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: _____.

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

5. ☐ A SUBSTITUTE OATH OR DECLARATION must be submitted. Note the attached EXAMINER'S AMENDMENT or NOTICE OF INFORMAL PATENT APPLICATION (PTO-152) which gives reason(s) why the oath or declaration is deficient.

6. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   (a) ☐ including changes required by the Notice of Draftsperson's Patent Drawing Review (PTO-948) attached
      1) ☐ hereto or 2) ☐ to Paper No./Mail Date _____.
   (b) ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____.

   Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).

7. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☒ Notice of References Cited (PTO-892)
2. ☐ Notice of Draftperson's Patent Drawing Review (PTO-948)
3. ☒ Information Disclosure Statements (PTO-1449 or PTO/SB/08), Paper No./Mail Date 11/17/03, 12/5/03,
4. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material
5. ☐ Notice of Informal Patent Application (PTO-152)
6. ☐ Interview Summary (PTO-413), Paper No./Mail Date _____ .
7. ☒ Examiner's Amendment/Comment
8. ☒ Examiner's Statement of Reasons for Allowance
9. ☐ Other _____.

EXAMINER'S AMENDMENT

An examiner's amendment to the record appears below. Should the changes and/or additions be unacceptable to applicant, an amendment may be filed as provided by 37 CFR 1.312. To ensure consideration of such an amendment, it MUST be submitted no later than the payment of the issue fee.

Authorization for this examiner's amendment was given in a telephone interview with Brian Del Buono on 1/6/2005, after a personal interview organized to discuss possible allowance of nicotine and cocaine embodiments. During the course of the discussion further embodiments were discussed. These embodiments were ultimately determined to be similarly nonobvious and enabled, as indicated in the examiner's amendment and reasons for allowance below.

The application has been amended as follows:

Claims 1-115 have been cancelled in favor of new claims 116-153 as shown on the attached claim listing.

The following is an examiner's statement of reasons for allowance:.

Swain et al, Cerny et al, Schiller et al, and Fehr et al are cited as the closest prior art. Cerny broadly teaches drug treatment using an immunogenic drug hapten-carrier conjugate, see the claims. Cerny does not teach an RNA phage virus-like particle as carrier. Swain teaches conjugation of nicotine or cocaine to a carrier protein, and teaches animal studies showing induction of antibodies using the conjugate and physiological changes including decreased drug entry into the brain after immunization.

Swain teaches a variety of carrier proteins including a yeast virus-like particle, but does not teach an RNA phage virus-like particle. Fehr teaches use of an RNA phage virus-like particle as an immunogenic carrier for a peptide hapten, but teaches fusion rather than chemical conjugation. Schiller teaches chemical conjugation of antigens to virus-like particles and teaches RNA phage particles, but teaches production of autoantibodies, not antibodies against a drug of abuse. Absent hindsight, the art of record does not provide particular motivation to combine the teachings of the various references to reach the invention as claimed.

The prior art indicates a high level of knowledge for RNA phage particles and also a high level of knowledge for chemical conjugation of the claimed drugs to other carrier proteins. Therefore undue experimentation is not required to make the invention as claimed. In regard to use of the invention, the art of record indicates that several drug immunoconjugates were in clinical trials for control of drug abuse. The prior art also indicates that immunoconjugates were commonly used to induce antibodies useful for drug detection. Therefore use of the invention does not require undue experimentation.

Any comments considered necessary by applicant must be submitted no later than the payment of the issue fee and, to avoid processing delays, should preferably accompany the issue fee. Such submissions should be clearly labeled "Comments on Statement of Reasons for Allowance."

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mary E. Mosher, Ph.D. whose telephone number is 571-272-0906. The examiner can normally be reached on M-T and alternate F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel can be reached on 571-272-0902. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

1/6/05

MARY E. MOSHER
PRIMARY EXAMINER
GROUP ~~1800~~ 1600

LISTING OF ALL CLAIMS

1-115 (cancelled).

116. A hapten-carrier conjugate comprising:

(a) a virus-like particle of an RNA phage, comprising at least one first attachment site, and

(b) at least one drug of abuse hapten with at least one second attachment site;

wherein said second attachment site is associated through at least one covalent bond to said first attachment site so as to form an ordered and repetitive hapten-carrier conjugate,

and wherein said drug of abuse is selected from the group consisting of:

(i) codeine;

(ii) fentanyl;

(iii) heroin;

(iv) morphine;

(v) amphetamine;

(vi) cocaine;

(vii) methylenedioxymethamphetamine;

(viii) methamphetamine;

(ix) methylphenidate;

(x) nicotine;

(xi) cotinine;

(xii) nornicotine;

(xiii) PCP;

(xiv) LSD;

(xv) mescaline;

(xvi) psilocybin;

(xvii) tetrahydrocannabinol;

(xviii) diazepam;

(xix) desipramine;

(xx) imipramine;

(xxi) nortriptyline; and

(xxii) the amitriptyline class of drugs.

117. The conjugate of claim 116, wherein said drug of abuse hapten is a nicotine hapten or a cocaine hapten.

118. The conjugate of claim 116, wherein said RNA phage is selected from the group consisting of:

(a) bacteriophage Qβ;

(b) bacteriophage R17;

(c) bacteriophage fr;

(d) bacteriophage GA;

(e) bacteriophage SP;

(f) bacteriophage MS2;

(g) bacteriophage M11;

(h) bacteriophage MX1;

(i) bacteriophage NL95;

(j) bacteriophage f2;

(k) bacteriophage AP205; and

(l) bacteriophage PP7.

119. The conjugate of claim 116, wherein said virus-like particle of an RNA phage comprises recombinant proteins of RNA phage Qβ.

120. The conjugate of claim 116, wherein said virus-like particle of an RNA phage comprises recombinant proteins of RNA phage fr.

121. The conjugate of claim 116, wherein said virus-like particle of an RNA phage comprises recombinant proteins of RNA phage AP205.

122. The conjugate of claim 116, wherein said virus-like particle of an RNA phage comprises recombinant proteins, or fragments thereof, of an RNA phage.

123. The conjugate of claim 116, wherein said virus-like particle of an RNA phage comprises one or more proteins having an amino acid sequence selected from the group consisting of:

(a) SEQ ID NO:3;

(b) a mixture of SEQ ID NO:3 and SEQ ID NO:4;

(c) SEQ ID NO:24;

(d) SEQ ID NO:25;

(e) SEQ ID NO:26;

(f) SEQ ID NO:27;

(g) a mixture of SEQ ID NO:27 and SEQ ID NO:28;

(h) SEQ ID NO:29;

(i) SEQ ID NO:30;

(j) SEQ ID NO:31;

(k) SEQ ID NO:32;

(l) SEQ ID NO:33;

(m)SEQ ID NO: 13; and

(n) SEQ ID NO: 14.

124. The conjugate of claim 123, wherein said virus-like particle of an RNA phage comprises SEQ ID NO:3 or a mixture of SEQ ID NO:3 and SEQ ID NO:4.

125. The conjugate of claim 123, wherein said virus-like particle of an RNA phage consists essentially of SEQ ID NO:3 or a mixture of SEQ ID NO:3 and SEQ ID NO:4.

126. The conjugate of claim 116, wherein said virus-like particle of an RNA phage comprises one or more coat proteins of said RNA phage modified by deletion or substitution to remove at least one naturally occurring lysine residue, or that have been modified by insertion or substitution to add at least one lysine residue.

127. The conjugate of claim 126, wherein said RNA phage is Qβ.

128. The conjugate of claim 127, wherein said virus-like particle comprises one or more proteins having an amino acid sequence selected from the group consisting of:

(a) SEQ ID NO:6;

(b) SEQ ID NO:7;

(c) SEQ ID NO:8;

(d) SEQ ID NO:9; and

(e) SEQ ID NO: 10.

129. The conjugate of claim 127, wherein the virus-like particle consists essentially of one or more proteins having an amino acid sequence selected from the group consisting of:

(a) SEQ ID NO:6;

(b) SEQ ID NO:7;

(c) SEQ ID NO:8;

(d) SEQ ID NO:9; and

(e) SEQ ID NO: 10.

130. The conjugate of claim 116, wherein said first attachment site comprises:

(a) an amino group;

(b) a carboxyl group;

(c) a sulfhydryl group;

(d) a hydroxy group;

(e) a guanidinyl group; or

(f) a histidinyl group.

131. The conjugate of claim 116, wherein said first attachment site is selected from the group consisting of a lysine residue, an arginine residue, a cysteine residue, an aspartate residue, a glutamate residue, a serine residue, a threonine residue, a histidine residue and a tyrosine residue.

132. The conjugate of claim 116, wherein said first attachment site is a lysine residue.

133. The conjugate of claim 116, wherein said conjugate is formed from starting materials selected from the group consisting of

(a) 6-(carboxymethylureido)-(±)-nicotine (CMUNic);

(b) trans-3'-aminomethylnicotine succinate;

(c) O-succinyl-3'-hydroxymethyl-nicotine;

(d) Trans-4'-carboxycotinine;

(e) N-[1-oxo-6-[(25)-2-(3-pyridyl)-1-pyrrolidinyl] hexyl]-β-alanine;

(f) 4-oxo-4-[[6-[(5S)-2-oxo-5-(3-pyridinyl)-1-pyrrolidinyl]]hexyl] amino]-butanoic acid;

(g) (2S)-2-(3-pyridinyl)-1-pyrrolidinebutanoic acid phenylmethyl ester;

(h) (2R)-2-(3-pyridinyl)-1-pyrrolidinebutanoic acid phenylmethyl ester;

(i) Cotinine 4'-carboxylic acid, N-succinyl-6-amino-(±)-nicotine;

(j) 6-(.sigma.-aminocapramido)-(±)-nicotine;

(k) 6-(.sigma.-aminocapramido)-(±)-nicotine;

(l) 3'-aminomethylnicotine;

(m) 4'-aminomethylnicotine;

(n) 5'-aminomethylnicotine;

(o) 5 -aminonicotine;

(p) 6-aminonicotine;

(q) S-1-(b-aminoethyl) nicotinium chloride; and

(r) S-1-(b-aminoethyl) cotinium chloride.

134. The conjugate of claim 116, wherein said hapten comprises the starting material O-succinyl-3'-hydroxymethyl-nicotine.

135. The conjugate of claim 116, wherein said conjugate comprises O-succinyl-3'-hydroxymethyl-nicotine conjugated to a Qβ virus-like particle.

136. The conjugate of claim 116, wherein said hapten is formed from the starting material O-succinyl-3'-hydroxymethyl-nicotine.

137. The conjugate of claim 116, wherein the second attachment site contains an active group selected from the group consisting of (a) Amine; (b) Amide; (c) Carboxyl; (d) Sulfhydryl; (e) Hydroxyl; (f) Aldehyde; (g) Diazonium; (h) Acylhalogen; (i) Hydrazine; (j) Vinyl; (k) Maleimide; (l) Succinimide; and (m) Hydrazide.

138. The conjugate of claim 137, wherein said second attachment site is formed by reaction of the O-succinyl moiety of said O-succinyl-3'-hydroxymethylnicotine with said first attachment site.

139. The conjugate of claim 137, wherein said second attachment site contains an amide.

140. The conjugate of claim 137, wherein said second attachment site is formed by reaction of the O-succinyl moiety of said O-succinyl-3'-hydroxymethylnicotine and wherein said first attachment site is a lysine residue.

141. The conjugate of claim 116, wherein said conjugate is formed from starting materials selected from the group consisting of (a) diazonium salt of benzoyl cocaine; (b) diazonium salt of benzoyl ecognine; (c) acylated ecgonine methyl ester; (d)

succinylated ecgonine methyl ester; (e) succinylated norcocaine; (f) Norcocaine; and (g) benzoyl ecgonine.

142. The conjugate of claim 141, wherein said second attachment site contains an active group selected from the group consisting of (a) Amine; (b) Amide; (c) Carboxyl; (d) Sulfhydryl; (e) Hydroxyl; (f) Aldehyde; (g) Diazonium; (h) Acylhalogen; (i) Hydrazine; (j) Vinyl; (k) Maleimide; (l) Succinimide; and (m) Hydrazide.

143. A composition suitable for inducing an immune response against a drug of abuse, comprising an effective immunogenic amount of the conjugate of claim 116 and a pharmaceutically acceptable carrier or excipient.

144. The composition of claim 143, further comprising an adjuvant.

145. The composition of claim 143, wherein the composition is devoid of an adjuvant.

146. A method of inducing an immune response against a drug of abuse, said method comprising administering to an individual the composition of claim 143.

147. A method of inducing an immune response against a drug of abuse, said method comprising administering to an individual the composition of claim 144.

148. A method of inducing an immune response against a drug of abuse, said method comprising administering to an individual the composition of claim 145.

149. The method of any one of claims 146-148, wherein said conjugate is administered to said individual by a route selected from the group consisting of intranasally, orally, subcutaneously, transdermally, intramuscularly and intravenously.

150. The method of claim 149, wherein the route is intranasal.

151. The method of claim 149, wherein said method comprises two or more immunizations of said individual with said conjugate.

152. The method of claim 151, wherein the immunizations are by the same route.

153. The method of claim 151, wherein the immunizations are by different routes.